REMARKS

Claims 1-7, 18 and 29-34 are pending. Claims 1, 30 and 34 have been amended. The amendments to the claim were made solely to expedite prosecution of the present application. No new matter has been added.

Objection to the Finality of the Office Action

Applicants respectfully object to the finality of the office action mailed April 19, 2001. As provided in the Manual of Patent Examining Procedures 706.07(a),

> a second or any subsequent action on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor base on information submitted in an information disclosure statement . . . (emphasis added).

The claims as pending prior to the Response filed March 20, 2001 contained claims directed to nucleic acid molecules having a specified level of sequence identity (i.e., 60% sequence identity) to the sequences listed in the claims. For example, claim 1 as originally filed contained this language. In the office action dated September 20, 2000, the Examiner did not reject the claims under 35 U.S.C §112, first paragraph as being non-enabled.

Claim 1 was only amended in the Response filed March 20, 2001 to increase the level of sequence identity between the nucleic acid molecule and the sequences listed in the claim. Clearly, this amendment did not change the claim in such a way as to necessitate a new ground for rejection for lack of enablement. However, the Examiner did add a new ground for rejection in the office action mailed April 19, 2001. (There was also no information disclosure statement filed in the interim of the Response filed March 20, 2001 and the Office Action mailed April 19, 2001). If the Examiner deemed a lack of enablement rejection necessary, the Examiner should have raised it in the first office action of September 20, 2000, either that or the office action mailed April 19, 2001 should not have been final. Therefore, Applicants point out that the finality of the April 19, 2001 office action is improper, and ask that the Examiner withdraw the finality of that action.

Rejection of Claims 1 and 2 Under 35 U.S.C. §102(a)

Claims 1 and 2 are rejected under 35 U.S.C. §102(a) as being anticipated by Robertson et al. (Genomics, December 1997).

Applicants respectfully request that the Examiner withdraw this rejection in view of the executed *In re* Katz Declaration by Cynthia Morton, Ph.D. submitted on herewith.

Rejection of Claims 1 and 2 Under 35 U.S.C. §102(a)

Claims 1 and 2 are rejected under 35 U.S.C. §102(a) or 102(b), depending on the date of availability, as being anticipated by sequence AF006741 (GenBank/EMBL, directed submission, 4 June 1997) and sequence AF006740 (GenBank/EMBL, direct submission, 4 June 1997).

Applicants respectfully request that the Examiner withdraw this rejection in view of the executed *In re* Katz Declaration by Cynthia Morton, Ph.D. submitted on herewith. As noted in this Declaration, Applicants submitted GenBank/EMBL Accession Numbers AF006741 and AF006740 prior to the publication of the Robertson et al. reference discussed above, however, these sequences were not made available on GenBank until after the publication of Robertson et al. (1997).

Rejection of Claims 1-7 Under 35 U.S.C.§103(a)

Claims 1-7 are rejected under 35 U.S.C. §103(a) as being "unpatentable over Robertson et al. (Genomic, December 1997) in view of the Pharmacia Catalog (1996).

Applicants respectfully request that the Examiner withdraw this rejection in view of the executed *In re* Katz Declaration by Cynthia Morton, Ph.D. submitted on herewith.

Rejection of Claims 1, 30, 32 and 34 Under 35 U.S.C. §112, first paragraph

Claims 1, 30, 32 and 34 are rejected under 35 U.S.C. §112, first paragraph based on written description and enablement issues. Each of these rejections is addressed below.

With regards to written description, the Examiner states that

> [t]he claims are drawn to a naturally occurring allelic variant of SEQ ID NO:2 and to nucleic acid sequences that share 85% sequence identity with SEQ ID NO:1, 90% sequence identity with SEQ ID NO:3 and to amino acid sequences that share 85% with SEQ ID NO:2. The specification discloses an isolated cDNA sequence SEQ ID NO:3 and SEQ ID NO:1, which encodes a predictive polypeptide sequence, SEQ ID NO:2. The broadly claimed allelic variants and sequences that share sequence similarity could include proteins that are functionally similar. The instant disclosure of a single species of nucleic acid coding for a single polypeptide does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Claiming that the allelic variants as having biologically activity does not overcome the instant written description rejection because neither the art in general nor the specification provide sufficient descriptive information, such as definitive structural or functional features of the claimed polypeptide and it's biologically activity. It appears that the biological activity of the instantly claimed COCH5B2 is based on homology modeling with the von Willibrandt factor. Homology modeling without actual verification of biological activity is insufficient to ascribe a particular activity . . . There is no description of sites at which variability may be tolerated and there is no information regarding the relation of structure and function.

Applicants respectfully traverse this rejection. Claims 1 and 34, as amended, are directed to a nucleic acid which encodes a polypeptide having at least on COCH5B2 activity and having at least 85% sequence identity to a nucleotide sequence of SEQ ID NO:1 or a complement thereof, or at least 90% sequence identity with SEQ ID NO:3 or a complement thereof. Claim 30, as amended, is directed to an isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence having at least about 85% sequence identity to the amino acid sequence of SEQ ID NO:2 and having at least one COCH5B2 activity. Claim 32 is directed to a nucleic acid molecule which encodes a naturally occurring allelic variant of COCH5B2, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1 or SEQ ID NO:3 under stringent conditions. There is clearly sufficient description provided in the present application for these claimed nucleic acid molecules.

The Examiner's arguments with regard to the amount of description provided in the present application are clearly erroneous. For example, the Examiner argues that "a single species does not adequately describe the claimed genus." However, the present application provides two different species of COCH5B2, namely human and mouse COCH5B2. Applicants obtained the murine COCH5B2 by screening a mouse cDNA library for sequences which bound

to a portion of the human COCH5B2 nucleic acid sequence under stringent hybridization conditions. Applicants also provide an alignment between these two proteins and the sequences encoding them and reports that the nucleotide sequences encoding human and murine COCH5B2 share 89% sequence identity, and the amino acid sequence of human and murine COCH5B2 share 94% sequence identity. See page 14 and Figure 3 of the present application.

The Examiner also wrongly asserts that the claimed biological activity is based solely on homology modeling with von Willebrand factor. This is clearly not the case. The biological activities of COCH5B2 are based on several levels of analysis described throughout the present application. For example, the one of the biological activities of COCH5B2 is interaction with extracellular matrix components COL1A2 and COL1A3. Applicants not only demonstrate homology between the von Willebrand factor domain of these collagens and COCH5B2, but also demonstrate expression of COL1A2, COL1A3 and COCH5B2 at similar levels in the cochlear. See page 13 of the present application. Another biological activity of COCH5B2 provided in the present application is the modulation of the production of acidophillic deposits in the ear. Applicants have demonstrated not only that COCH5B2 is associated with DFNA9 (which results in acidophillic deposits in the ear) but also that COCH5B2 and these acidophillic deposits show parallel expression patterns in the ear. Thus, Applicants have clearly shown more than just homology of the vWF domain to support the activities of COCH5B2.

The Examiner also incorrectly asserts that there is "no disclosure of sites at which variability may be tolerated." Throughout the present application, Applicants provide comparisons of the sequences of murine and human COCh5B2, describe the conserved domains of this protein, describe various conservative substitutions, and explicitly point out areas of the COCH5B2 sequences which may tolerate variability. For example, pages 23-25 of the present application provide various regions of the COCH5B2 that are likely to be amenable to alteration without effecting COCH5B2 activity. See also page 70 which discusses the homology between sequence encoding human and murine COCH5B2 and points out that the homology between these two sequences drops abruptly in the 3' untranslated region.

In view of the fact that Applicants have provided more than one species of COCH5B2, have repeatedly pointed out structural similarities between these sequences, and have demonstrated an association of several of these structural features to COCH5B2 biological

activities, Applicants have clearly provided sufficient description of the claimed nucleic acid molecules. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner also rejected claims 1, 30, 32 and 34 asserting non-enablement. In particular, the Examiner states that

> [t]he specification while being enabling for SEQ ID NO:1-3 does not provide enablement for the other sequences that share a specific percent identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.
>
> The specification discloses CHOCH5B2 protein with SEQID No 2 and the corresponding nucleic acid of SEQ ID No 1. It would be an undue burden for one of skill in the art to practice the claimed invention in terms of making all of the homologous sequences from the disclosed sequences because the specification provides no guidance as to the many different homologous sequence that can be produced. A 85% homology of SEQ ID NO:1 corresponds to a nucleotide difference of 256 nucleotides, similarly a 90% homology of SEQ ID NO:3 corresponds to a nucleotide difference of 165 nucleotides, while a 85% homology of SEQ ID NO:2 corresponds to an amino acid difference of 82 amino acids. These nucleotide and amino acid sequence substitutions can be arranged contiguously or sparsely at different positions on a sequence. The state of the art is such that one can not predict what substitution will result in significant structural or functional changes . . . There is no guidance in the specification to teach where the sequence should be substituted, and therefore, the functionality of the protein would be unpredictable. Moreover, one of skill in the art would not know which positions of the substitution would retain the characteristics of COCH5B2 without undergoing extensive experimentation. Therefore, the instant specification is not enabled for the scope of the claims.

Applicants respectfully traverse this rejection. The present application clearly provides sufficient guidance to enable a skilled artisan to obtain nucleic acid molecules having high levels of sequence identity with the sequences listed in the claims. First of all, Applicants point out that there is more than one COCH5B2 disclosed in the present application. Applicants have provided the nucleotide and amino acid sequence of both human and murine COCH5B2. In addition, Applicants have provided alignments between these sequences (see, e.g., Figure 3 of the present application), have provided regions that are highly conserved between these sequence (see, e.g., pages 70-71 of the present application), have disclosed regions of these sequence likely to be

amenable to alteration (see, e.g., pages 23-25, and pages 70-71 of the present application). Applicants have also provided several activities for COCH5B2 which can easily be assayed to confirm function of the encoded COCH5B2 polypeptide. For example, COCH5B2 activities include interaction with COL1A2 and COL1A3. Using routine binding assays, it can be determined if an encoded polypeptide retains such activities. Based on such information, a skilled artisan would clearly be able to make and use the claimed nucleic acids without undue experimentation.

This point is further exemplified in the present application by the fact that Applicants provide an example of obtaining such a nucleic acid using routine screening techniques. For example, at page 64, Applicants describe obtaining the nucleotide sequence of murine COCH5B2 by screening a murine cDNA library using portion of the human COCH5B2 nucleic acid sequence under stringent hybridization conditions. The isolated murine COCH5B2 nucleic acid molecule was shown to have 89% sequence identity with the human COCh5B2 nucleic acid sequence and the amino acid sequence of murine COCH5B2 was shown to share 94% sequence identity with the amino acid sequence of human COCH5B2. Thus, using the methods provided in the present application, a skilled artisan could easily screen for nucleic acid molecules having the specified level of homology to the sequences listed in the claims without undue experimentation.

Therefore, for the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 5/24/01

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Version with markings to show changes made

In the claims:

Claims 1, 30, and 34 have been amended as follows:

1. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence which has at least 85% sequence identity to a nucleotide sequence of SEQ ID NO:1, or a complement thereof, and which encodes a polypeptide having at least on COCH5B2 activity.

30. (Amended) An isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence having at least about 85% sequence identity to the amino acid sequence of SEQ ID NO:2 and having at least one COCH5B2 activity.

34. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence which has at least 90% sequence identity to a nucleotide sequence of SEQ ID NO:3, or a complement thereof, and which encodes a polypeptide having at least one COCH5B2 activity.--